A comparison of vaginal versus buccal misoprostol for cervical ripening in women for labor induction at term (the IMPROVE trial): a triple masked randomized controlled trial

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Condensation

In leading to a higher rate of vaginal deliveries and more rapid vaginal delivery, vaginal misoprostol may be superior to buccal misoprostol for cervical ripening at term.

Implications and Contributions/ AJOG at a Glance

A. Why was this study conducted?
    - Buccal misoprostol is being used more commonly for cervical ripening but has not been well studied
    - Retrospective data indicated buccal misoprostol might be non-inferior to vaginal misoprostol

B. What are the key findings?
    - We did not find buccal misoprostol to be non-inferior to vaginal misoprostol
    - Women in the vaginal misoprostol group had higher rates of vaginal delivery, more rapid times from induction to deliveries, and fewer cesareans for fetal heart rate abnormalities

C. What does this study add to what is already known?
    - Vaginal misoprostol may be superior to buccal misoprostol
    - There were no differences in preference for buccal or vaginal misoprostol routes for women in the trial.

Short title

IMPROVE trial- buccal versus vaginal misoprostol for cervical ripening

Abstract

Background: Cervical ripening is commonly needed for labor induction. Finding an optimal route of misoprostol dosing for efficacy, safety, and patient satisfaction is important and not well studied for the buccal route.

Objective: To compare the efficacy and safety of vaginal and buccal misoprostol for women undergoing labor induction at term.

Study Design: The IMPROVE trial was an IRB-approved, triple-masked, placebo-controlled randomized non-inferiority trial for women undergoing labor induction at term with a Bishop's Score ≤ 6. Enrolled women received 25 mcg (1st dose), then 50 mcg (subsequent doses) of misoprostol by assigned route (vaginal [VM] or buccal [BM]) and a matching placebo tablet by the opposite route. The primary outcomes were time to delivery and the rate of cesarean delivery performed urgently for fetal non-reassurance. A sample size of 300 was planned to test the non-inferiority hypothesis.

Results: The trial enrolled 319 women, with 300 available for analysis, 152 VM and 148 BM. Groups had similar baseline characteristics. We were unable to demonstrate non-inferiority. The time to vaginal delivery was lower for the VM group (median [95% confidence interval] in hours: VM: 20.1 [18.2, 22.8] vs. BM: 28.1 [24.1, 31.4], Log-rank test p=0.006, $p_{non\text{-}inferiority} = 0.663$). The rate of cesarean deliveries for non-reassuring fetal status was 3.3% for the VM group and 9.5% for the BM group (p=0.033). The rate of vaginal delivery in <24 hours was higher in the VM group (58.6% vs. 39.2%, p=0.001).

Conclusion: We were unable to demonstrate non-inferiority. In leading to a higher rate of vaginal deliveries, more rapid vaginal delivery, and fewer cesareans for fetal issues, vaginal misoprostol may be superior to buccal misoprostol for cervical ripening at term.

Trial Registration: clinicaltrials.gov (NCT02408315)

Key Words: buccal, cervical ripening, labor induction, misoprostol, term pregnancy, vaginal

Introduction

The rate of labor induction has doubled over the last 25 years, with nearly 25% of gravid women undergoing labor induction in the United States.[1] The goal of induction of labor is to achieve vaginal delivery by stimulating uterine contractions, cervical dilation, and active labor. Labor is typically induced when the risks of continuing the pregnancy outweigh the risks of delivery or labor induction.[2]

Often when labor is induced, the cervix must be "ripened", a process involving cervical softening, thinning, and dilation to help facilitate the successful induction of labor.[2] Prostaglandins have been effectively utilized for cervical ripening and labor induction for decades as they induce both cervical changes and stimulate uterine contractions.[3] Misoprostol, a synthetic prostaglandin E1 analogue, has been shown to be an effective and safe drug for induction and is the most frequently used induction method.[2, 4, 5] According to both the World Health Organization and the American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin on Induction of Labor, doses of 25 mcg and higher are typically administered every 4-6 hours, depending on provider preference.[2]

Misoprostol is currently administered in many different ways.[6] It can be administered vaginally, rectally, orally, buccally, and sublingually.[7, 8] While vaginal administration of misoprostol is most common, recent trends in practice have shifted toward more buccal use of this drug. A recent survey found that midwives indicted a preference toward buccal dosing.[9] However, only one published trial directly compared buccal to vaginal misoprostol.[10] In that trial of 157 women, there were no significant differences in any of the outcomes other than higher rates of tachysystole in the buccal group. However, that trial utilized higher doses of misoprostol (up to 100mcg) than are typically used clinically.[2] A recent retrospective cohort study of 207 women also found that time to delivery may be similar for the two routes of administration.[11] Clinical experience at our center and these retrospective observations led to a hypothesis that the two routes were clinically equivalent. Given that if buccal was not inferior clinically to vaginal dosing and that patients may prefer avoiding additional vaginal examinations to place medication, a non-inferiority trial was warranted.

The primary objective of the Induction with MisoPRostol: Oral mucosa versus Vaginal Epithelium (IMPROVE) study was to compare the efficacy and safety of vaginal and buccal misoprostol for women undergoing labor induction at greater than or equal to 37 completed weeks gestation with a live fetus.

Materials and Methods

The IMPROVE trial was a triple-blinded, placebo controlled study conducted from August 2015 through October 2017 at two hospitals in Indianapolis, IN served by the Indiana University (IU) School of Medicine Department of OB/GYN and the physicians and certified nurse midwives of the HealthNet medical group. The first participant was enrolled 10/4/2015 and the final participant was enrolled 10/3/2017. This study was a triple masked, randomized controlled trial for inpatient women on labor and delivery receiving misoprostol for cervical ripening during labor induction. Funding for the study was provided by the IU Department of OB/GYN. The trial was conducted under a U.S. Food and Drug Administration Investigational New Drug application (IND#: 122727), was approved by the IU IRB, and was registered on clinicaltrials.gov (NCT 02408315). A Data & Safety Monitoring Board reviewed blinded results for efficacy and safety after recruitment of 50 women, 150 women, and at trial completion. The full details of the Methods of the study are presented in Supplementary Material.

Participants

Women who presented to the labor and delivery unit for delivery who required cervical ripening were eligible for the trial. Women ≥14 years of age undergoing either a medically indicated induction of labor at a gestational age beyond $37^{0/7}$ weeks or an elective induction of labor after 39 weeks with a singleton pregnancy in the cephalic presentation, and a modified Bishop score ≤ 6 (commonly used as a cutoff for the need for cervical ripening) were eligible for enrollment. Women were excluded if they had a known prior uterine scar, untreated cervical infection, known major fetal congenital anomaly, or evidence of fetal compromise (Category 2 or 3 fetal tracing) before the start of the induction. All women underwent the informed consent.

Study drugs and preparation

Misoprostol tablets (100 micrograms) were obtained from the manufacturer (Novel Laboratories, Somerset, NJ). Identical placebo tablets were obtained from University of Iowa Pharmaceuticals. Tablets were divided in half or quarters (25 or 50 microgram doses) by the Investigational Pharmacies and packaged in identical foil packets labeled either "Vaginal" or "Buccal".

Randomization and allocation concealment

Computer-generated, stratified randomization with blocks of size 10 was used for each hospital with 1:1 assignment to treatment group. After informed consent was obtained by the study team, the appropriate Investigational Pharmacy was notified. The pharmacist on duty obtained the next sequentially numbered study drug packet and sent it to labor and delivery. Other than the investigational pharmacist, who did not have direct subject contact, no investigators, providers or patients had knowledge of randomization assignment.

Study procedures

After obtaining informed consent and obtaining study drugs in air-tight foil packs from the pharmacy, the tablet marked "Buccal" was placed between the teeth and mucous membrane of the cheek and the tablet marked "Vaginal" was placed by the clinical care provider high into the posterior vaginal fornix. The initial dose of misoprostol used in this protocol was 25 mcg. Subsequent doses, if utilized, were 50 mcg in accordance with the ACOG Practice Bulletin.[2] Throughout the cervical ripening and induction process, continuous external electronic fetal monitoring was utilized as per standard hospital practice.

Cervical examinations were performed approximately every four hours, prior to buccal and vaginal administration of the next dose. An additional dose (50 mcg) of study drug was given if clinically indicated. Study participation and drug placement continued until there was either: 1) adequate response and cervical ripening was no longer needed, 2) signs of tachysystole, non-reassuring fetal heart tracing, or other adverse event that would make the provider stop the misoprostol, or 3) 24 hours of study drug given (maximum of 7 doses). After cervical ripening was complete or the participant was taken off of the study,

there were no limitations placed on the clinical care. At least 30 days after delivery, data was abstracted from the medical record to capture all relevant maternal and newborn outcomes and complications.

Outcomes assessment

The primary efficacy outcome was the time to delivery, defined as the time from placement of the first dose of study drug to the time of delivery. The primary safety outcome was the rate of cesarean delivery performed urgently for fetal non-reassurance as the primary indication, however the study was not powered for this outcome. Secondary efficacy and safety outcomes included typical outcomes during labor and delivery, such as labor characteristics and other medications used (for full list, see Supplementary Material). The IMPROVE trial also assessed participant satisfaction with a modified tool from Nassar.[12]

At least 30 days after delivery, the medical records of the participant and her newborn were reviewed and data abstracted from the medical record to capture all relevant maternal and newborn outcomes and complications.

Statistical analysis and sample size calculations

The study was planned as a non-inferiority trial to assess the primary outcome of time to delivery. This was based on our retrospective study finding similar times to delivery.[11] Our data found that the median time to delivery with both buccal and vaginal misoprostol was about 18 hours. If the buccal route was non-inferior, we hypothesized that participant discomfort would be less with buccal as additional vaginal examinations might be avoided. A sample size of 300 women with 260 expected vaginal deliveries[11] was estimated to have 80% power to test a null hypothesis that the hazard ratio (HR) of BM relative to VM would be ≤ 0.74 vs alternative hypothesis that the HR > 0.74 with type I error set at 0.05. This non-inferiority margin was derived from retrospective data on time to delivery by both routes, which equated to approximately a 4.5 hour difference in median time to delivery. For all other outcomes, the two-sided superiority p-values are provided.

Participant and delivery characteristics were compared between treatment groups using appropriate tests (T-test, Wilcoxon rank sum test, Chi-square test, or Fisher's exact test). For the primary

outcome of time to delivery, median time to delivery and associated 95% confidence intervals (CI) were estimated by Kaplan-Meier method for the overall cohort and by route of delivery. The time to vaginal delivery for women who required cesarean delivery was censored at the time of cesarean. Cox proportional hazards regression was used to estimate the HR for BM relative to VM for delivering vaginally and associated 95% CI. A p-value < .05 provides evidence to reject inferiority and conclude the buccal route of dosing is non-inferior to the vaginal route. In secondary analyses, the HR and associated 95% CI for route of misoprostol was also estimated from the Cox proportional hazards regression, adjusting for covariates known to be associated with time to delivery. All analyses were based on assigned group and completed with SAS software version 9.4 (SAS Institute, Inc. Cary, NC).

Results

Participant Characteristics

Of 329 women consented for the trial (Figure 1), ten were excluded before randomization, either because they withdrew their consent after signing or were found to not meet inclusion criteria on a secondary chart review in preparation for randomization. Thirteen randomized women (4%) did not receive the allocated intervention, most (8) because they developed an exclusion criteria before study drug placement, typically either fetal tracing abnormalities or cervical dilation change. Six women (2%) randomized and initially dosed were administratively withdrawn from analysis after later discovery of documentation or consent issues making them ineligible. This left 300 women (94% of those randomized) eligible for analysis, of whom 152 received VM and 148 received BM (Figure 1).

Demographic characteristics by treatment group are provided in Table 1. Overall, randomization achieved balanced groups. The most common indications for induction were late-term pregnancy (27%), hypertensive disorder (21%), and diabetes mellitus (10%). Hispanic women comprised 29% of the cohort and 31% of women were African-American. Forty-one percent of the women were nulliparous. The mean gestational age of both groups was just over 39 weeks. 242 women (80.7%) had a successful induction and delivered vaginally (Table 2). One woman in the trial was sent home after receiving a course of study drug, returned at a later date, and delivered vaginally; this participant was censored at

time of discharge for the primary outcome of time to delivery but was included in all other analyses. Reasons for stopping misoprostol use were typical for cervical ripening and included sufficient cervical ripening (34%), safety concerns- most commonly tachysystole or fetal heart tracing abnormalities (27%), active labor (6%), or multiple reasons together (23%) (Table 2).

Primary outcomes

The primary outcome of time to delivery from receipt of first dose of misoprostol was significantly longer for women receiving BM rather than VM (median [95% CI]; BM: 28.1 [24.1 to 31.4] hrs vs. VM: 20.1 [18.2 to 22.8] hrs, p = .006) (Table 2, Figure 2 Top Panel). Based on the Cox proportional hazards model, the BM vs. VM HR for vaginal delivery is 0.70 [0.54 to 0.90], thus our null hypothesis that the HR $\leq$ 0.74 is not rejected ($P_{\text{non-inferiority}} = 0.663$) and we cannot conclude BM is non-inferior to VM.

For the primary safety outcome, there was higher rate of urgent cesarean delivery for fetal non-reassurance in women receiving BM (n=14, 9.5%) vs. VM (n=5, 3.3%), p=0.033 (Table 2, Table S1).

Covariates known to be associated with time to delivery were included in a full Cox proportional hazards model to estimate the adjusted HR for BM vs. VM for time to delivery (Table 3). In the adjusted model, the BM vs. VM adjusted HR is 0.59, [0.45 to 0.77], p<0.0001 (Table 3). Thus, VM was found to be superior after adjustment for covariates. Although the assumption of proportional hazards was not rejected for this full model (P=0.062), the two-way interaction between parity and log of time to delivery and oxytocin and log of time delivery were both significant at the 0.05 level. Thus, we ran additional models to examine these important covariates (Supplemental Material). Multiparous women had a larger difference in median time to delivery between treatment groups compared to nulliparous women (Tables S3, S4, and Figure 2 Bottom Panel).

Secondary outcomes

The rate of vaginal delivery within 24 hours from start of induction was significantly higher in the VM group (58.6% vs. 39.2%, RR 1.49 [1.17 to 1.90], P=0.001). The number of doses of misoprostol required to achieve active labor was significantly less in the VM group (median [range]: 2 [1-5] vs. 3 [1-

7], P<0.001). The reason for stopping misoprostol was cited as sufficient cervical ripening more frequently for women in the VM group (39.5% vs. 29.1%, p=0.006). The maximum dose of oxytocin used during labor for women in the BM group was higher than for the VM group (6 mu/min vs. 4 mu/min, p=0.001). The overall rates of cesarean delivery were similar in the two groups (VM 15.8%, BM 22.3%, p=0.15). There were no other statistically significant differences in treatment groups on delivery characteristics (Table 2) or in maternal or fetal serious adverse events (Table S1).

Participant preferences

There were no differences in participant satisfaction responses obtained the first or second day after delivery regarding their experience with induction of labor, expectations on pain, comfort regarding route of misoprostol, route they liked better, or preference of route in future IOL (Table S5). When asked which way of giving the medication was more comfortable, 43% responded they were the same, 39% said in the cheek, and 13% said in the vagina. When asked which dosing location would they prefer for a future induction if both medication routes were equivalent, 41.7% [36.1% to 47.3%] preferred "in my cheek", 31.3% [26.1% to 36.6%] preferred "in my vagina", and 21.7% [17.0% to 26.3%] said they were not sure.

Structured Discussion/Comment

1. Principal Findings

In the IMPROVE trial, women receiving vaginal misoprostol, compared to buccal misoprostol, were more likely to deliver more rapidly, deliver vaginally within 24 hours, and require fewer doses of misoprostol to achieve active labor. The buccal misoprostol group had significantly more cesarean deliveries for fetal non-reassurance. There were no differences in other adverse safety events.

2. Results in context

Several systematic reviews have compared alternative routes of misoprostol use to the vaginal route.[13-15] Most have found similar effectiveness of non-vaginal routes. Buccal dosing of misoprostol cannot be assumed to be the same as the more studied sublingual dosing. Analysis of the pharmacokinetics of misoprostol given by buccal and sublingual routes clearly demonstrate differences.[16]

The onset of action of oral and sublingual routes are similarly fast (8-11 minutes) compared to vaginal route (20 minutes). However, most of the pharmacokinetic studies on misoprostol use high doses (600mcg or more) not typically used for labor induction. The Cochrane Review comparing buccal to vaginal dosing of misoprostol identified only one trial of buccal vs. vaginal misoprostol. However, it utilized different doses of misoprostol for each route of administration, making direct comparison impossible.[14] The authors concluded that larger efficacy and safety trials were required to evaluate the buccal route. This has been accomplished in our trial.

Our rates of serious adverse events were low and were mostly due to prolonged hospitalization. Rates of tachysystole requiring therapeutic intervention were 14% in the vaginal group and 12% in the buccal group- similar to rates found in some other trials.[12, 17] This is in contrast to the trial by Carlan et al. which demonstrated higher rates of misoprostol-induced hyperstimulation needing treatment in the buccal group (26%) than in the vaginal group (18%). However, that study used up to 300 mcg of buccal misoprostol but only 50 mcg vaginally.[10]

3. Clinical implications

As labor inductions are common, finding optimal methods to accomplish vaginal delivery is important. We have demonstrated that at typically used doses, vaginal misoprostol leads to more rapid deliveries and has fewer urgent cesarean deliveries for fetal distress than buccal dosing. Given the recent findings of the ARRIVE trial,[18] it is possible that the number of labor inductions will increase, further adding to the importance of optimizing this procedure.

Our subgroup analysis found that for multiparous women, vaginal dosing was superior to buccal dosing. This finding was true even after adjusting for other covariates such as the Bishop Score at trial entry. This may be due to biochemical differences in the cervices of nulliparous and multiparous women. Further investigation is warranted as subgroup analyses are exploratory, but it is possible that residual uterine and cervical factors from prior deliveries may make multiparous women more responsive to vaginal misoprostol. As nulliparous women frequently need cervical ripening, we plan to further explore

the potential equivalence of the dosing routes in this group. A trial powered for nulliparous women is warranted.

While we hypothesized that women undergoing labor induction would strongly prefer the medication by a non-vaginal route, we found similar rates of satisfaction with labor induction and dosing regimen preferences between groups. This is in contrast to previous, but non-blinded studies that have found participants prefer sublingual dosing.[12, 19] By administering study drug both buccally and vaginally in a blinded fashion, preferences were not different. Interestingly, the rate of women preferring to have the medication in the cheek for a future induction was not much higher than those preferring the vagina (42% vs. 31%, respectively). However, as the women were already anticipating cervical examinations, perhaps that led to a large number preferring vaginal dosing. In practice, however, when practitioners are not blinded to study drug as in our study, they may choose to skip some cervix examinations during cervical ripening with buccal dosing. This may have also influenced the route choice responses from participants. We did not specifically ask about the taste of the tablets, which also may have played a role in the responses.

4. Research Implications

We are currently exploring potential pharmacokinetic differences in the two dosing routes and the role they may play in outcomes from misoprostol. Further exploration of the differences in response of nulliparous and multiparous women is also warranted as providers attempt to individualize labor induction methods. A systematic comparison of available dosing and routes of misoprostol for labor induction is warranted that would include buccal dosing.

5. Strengths and Limitations

The major strength of our trial is that it had blinding of participants, providers, and study personnel/outcomes assessors (triple blinding), as well as during data analysis, which reduces bias as compared to prior trials. To our knowledge, this is one of only a few trials utilizing buccal misoprostol in the same dose as vaginal misoprostol for cervical ripening and labor induction at term for women with a live fetus. As many of our providers are uncomfortable placing vaginal drug in women with ruptured

membranes, we enrolled only one woman with ruptured membranes. Thus, our findings are essentially limited to women with intact membranes. Our study was stratified by site and differences between the populations at each site were accounted for in the analysis. But there could have been other differences in the two populations unaccounted for. Our findings of potential equivalence of the routes in nulliparous women is limited by this being a subgroup analysis not in the original power calculation.

6. Conclusions

In conclusion, we were unable to confirm non-inferiority of buccal vs. vaginal misoprostol. In fact, we found that vaginal misoprostol may be superior to buccal misoprostol for cervical ripening at term. However, an RCT specifically powered to detect a clinically meaningful difference for which to conclude superiority of vaginal misoprostol to buccal is still required. Vaginal dosing appears to lead to more rapid delivery and fewer cesareans for fetal distress.

Figure Legends

Figure 1. Consort diagram of participant flow through IMPROVE trial

Figure 2. Top Panel: Kaplan-Meier curves for time to delivery from start of induction in hours for all women in IMPROVE trial stratified by route of misoprostol. Bottom Panel: Kaplan-Meier curves for time to delivery for participants stratified by nulliparous (yes or no) and route of misoprostol. Women delivered by cesarean are censored at the time of that delivery. Numbers below the graphs are the number of women in each group still pregnant at that time point.

References

1. MARTIN JA, HAMILTON BE, OSTERMAN M, DRISCOLL AK, DRAKE P. Births: final data for 2016. Nat Vital Stat Rep 2018;67:1-55.
2. ACOG Practice Bulletin No. 107: Induction of labor. Obstet Gynecol 2009;114:386-97.
3. THOMAS J, FAIRCLOUGH A, KAVANAGH J, KELLY AJ. Vaginal prostaglandin (PGE2 and PGF2a) for induction of labour at term. Cochrane Database Syst Rev 2014:CD003101.
4. HOFMEYR GJ, GULMEZOGLU AM, PILEGGI C. Vaginal misoprostol for cervical ripening and induction of labour. Cochrane Database Syst Rev 2010:CD000941.
5. KRAUSE E, MALORGIO S, KUHN A, SCHMID C, BAUMANN M, SURBEK D. Off-label use of misoprostol for labor induction: a nation-wide survey in Switzerland. Eur J Obstet Gynecol Reprod Biol 2011;159:324-8.
6. ELATI A, WEEKS AD. The use of misoprostol in obstetrics and gynaecology. BJOG: An International Journal of Obstetrics & Gynaecology 2009;116:61-69.
7. STEPHENSON ML, WING DA. Misoprostol for induction of labor. Semin Perinatol 2015;39:459-62.
8. ALFIREVIC Z, KEENEY E, DOWSWELL T, et al. Methods to induce labour: a systematic review, network meta-analysis and cost-effectiveness analysis. BJOG 2016;123:1462-70.
9. TOWNS R, QUINNEY SK, PIERSON RC, HAAS DM. Survey of Provider Preferences Regarding the Route of Misoprostol for Induction of Labor at Term. AJP Rep 2017;7:e158-e62.
10. CARLAN SJ, BLUST D, O'BRIEN WF. Buccal versus intravaginal misoprostol administration for cervical ripening. American Journal of Obstetrics & Gynecology 2002;186:229-33.
11. DORR ML, PIERSON RC, DAGGY J, QUINNEY SK, HAAS DM. Buccal Versus Vaginal Misoprostol for Term Induction of Labor: A Retrospective Effectiveness Cohort Study [26K]. Obstetrics & Gynecology 2016;127:96S.
12. NASSAR AH, AWWAD J, KHALIL AM, ABU-MUSA A, MEHIO G, USTA IM. A randomised comparison of patient satisfaction with vaginal and sublingual misoprostol for induction of labour at term. Bjog 2007;114:1215-21.
13. ALFIREVIC Z, AFLAIFEL N, WEEKS A. Oral misoprostol for induction of labour. Cochrane Database Syst Rev 2014;6:CD001338.
14. MUZONZINI G, HOFMEYR GJ. Buccal or sublingual misoprostol for cervical ripening and induction of labour. Cochrane Database of Systematic Reviews 2004:CD004221.
15. SOUZA AS, AMORIM MM, FEITOSA FE. Comparison of sublingual versus vaginal misoprostol for the induction of labour: a systematic review. BJOG 2008;115:1340-9.
16. SCHAFF EA, DICENZO R, FIELDING SL. Comparison of misoprostol plasma concentrations following buccal and sublingual administration. Contraception 2005;71:22-5.
17. CALISKAN E, BODUR H, OZEREN S, CORAKCI A, OZKAN S, YUCESOY I. Misoprostol 50 microg sublingually versus vaginally for labor induction at term: a randomized study. Gynecol Obstet Invest 2005;59:155-61.
18. GROBMAN WA, RICE MM, REDDY UM, et al. Labor Induction versus Expectant Management in Low-Risk Nulliparous Women. N Engl J Med 2018;379:513-23.
19. ZAHRAN KM, SHAHIN AY, ABDELLAH MS, ELSAYH KI. Sublingual versus vaginal misoprostol for induction of labor at term: a randomized prospective placebo-controlled study. J Obstet Gynaecol Res 2009;35:1054-60.

Table 1: Demographic characteristics of women in the IMPROVE at study entry

Characteristic	*VM group (n= 152)*	*BM group (n= 148)*
Age – yr. Mean ±SD	28.2±6.4	27.6±6.4
Site – no. (%)		
Eskenazi	86 (56.6)	83 (56.1)
Methodist	66 (43.4)	65 (43.9)
Nulliparous women – no. (%)	59 (38.8)	65 (43.9)
Race/Ethnicity – no. (%)		
White	74 (48.7)	66 (44.6)
African American	45 (29.6)	49 (33.1)
Other	33 (21.7)	33 (22.3)
Ethnicity – no. (%)		
Hispanic/ Latino	42 (27.6)	44 (29.7)
Non-Hispanic /Non-Latino	109 (71.7)	99 (66.9)
Prefer not to Answer	1 (0.7)	5 (3.4)
BMI kg/m^2 Mean ±SD	35.7±7.2	35.1±7.3
BMI category – no. (%)		
<18	0	1 (0.7)
18-25	7 (4.6)	12 (8.1)
25-30	22 (14.5)	22 (14.9)
30-40	87 (57.2)	77 (52.0)
>40	36 (23.7)	36 (24.3)
Gestational age at trial entry weeks Mean ±SD	39.6 (1.3)	39.5(1.3)
Indication for induction – no. (%)		
Fetal Indications	10 (6.6)	17 (11.5)
Hypertensive disorder	33 (21.7)	31 (21.0)

Diabetes mellitus	10 (6.6)	20 (13.5)
Late-term pregnancy (≥ 41+0 weeks)	44 (29.0)	36 (24.3)
Elective	21 (13.8)	13 (8.8)
Multiple reasons	13 (8.6)	13 (8.8)
Other	21 (13.8)	18 (12.2)
Epidural – no. (%)	127 (83.6)	122 (82.4)
Cervical dilatation– no. (%)		
<1 cm	31 (20.7)	37 (25.2)
1-2 cm	102 (68)	89 (60.6)
>2 cm	17 (11.3)	21 (14.3)
Cervical dilatation cm Mean ±SD	1.3±0.9	1.3±0.9
Effacement of Cervix – no. (%)		
0-30% or > 4cm length	82 (54.7)	82 (55.8)
40-50% or 3-4 cm length	62 (41.3)	52 (35.4)
60-70% or 1-2 cm length	5 (3.3)	10 (6.8)
Effacement of cervix measure %. Mean ±SD	31.7±20.8	31.8±22.8
Fetal station (cm) – no. (%)		
-3	106 (72.1)	106 (72.6)
-2	34 (23.1)	36 (24.7)
-1,0	7 (4.8)	4 (2.7)
Fetal station cm Mean ±SD	-2.8±0.8	-2.8±0.7
Bishop score Mean ±SD	2.3±1.7	2.2±1.7

2 ***No statistically significant differences in any baseline characteristics between groups.***

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Table 2: Labor and delivery outcomes of women in IMPROVE study

	n = 152, 24 censored	n = 148, 34 censored	***P Value****	HR [95% CI]*	P Value$_{non\text{-}inferiority}$
Time to delivery (hours)– Median [95% CI]	20.1 [18.2, 22.8]	28.1 [24.1, 31.4]	0.006	0.70 [0.54, 0.90]	0.663
	VM group (n= 152)	***BM group (n= 148)***	***P Value†***		
Cesarean for Fetal non-reassurance– no. (%)	5(3.3)	14 (9.5)	0.033		
Vaginal delivery in less than 24 hours– no. (%)	89 (58.6)	58 (39.2)	0.001		
Reason for stopping misoprostol – no. (%)			0.006‡		
Onset of active labor	7 (4.6)	10 (6.8)			
Sufficient cervical ripening	60 (39.5)	43 (29.1)			
Safety concerns	47 (30.9)	34 (23)			
Multiple reasons	31 (20.4)	38 (25.7)			
Other	7 (4.6)	23 (15.5)			
Route of delivery– no. (%)			0.151		
Vaginal delivery	127** (84.2)	115 (77.7)			
Cesarean delivery	24 (15.8)	33 (22.3)			
Cesarean (indications) – no. (%)	**N = 24**	**N = 33**	0.376‡		
Fetal non-reassurance	5 (20.8)	14 (42.4)			
Arrest of dilation	3 (12.5)	4 (12.1)			
Arrest of descent	3 (12.5)	1 (3.0)			

Multiple reasons	11 (45.8)	11 (33.3)	
Other	2 (8.3)	3 (9.1)	
Chorioamnionitis– no. (%)	7 (4.6)	10 (6.8)	0.420‡
Postpartum hemorrhage– no. (%)	8 (5.3)	6 (4.0)	0.620‡
Blood transfusion– no. (%)	1 (0.6)	1 (0.7)	0.794‡
Oxytocin use– no. (%)	100 (65.8)	111 (75)	0.081
# doses of misoprostol needed to get into active labor Median (Range)	2.0 (1.0-5.0)	3.0 (1.0-7.0)	<0.001‡
Maximum units of oxytocin administered Median (Range)	4.0 (0 -36.0)	6.0 (0-30.0)	0.001‡

† P-Values obtained from T-Test (continuous) or Chi-square test (categorical). ‡ P-values obtained from Wilcoxon rank sum test (continuous) or Fishers' exact test (categorical). **One subject was admitted into the study, got discharged and then returned two weeks later to have a vaginal delivery. Delivery characteristics (except for route of delivery) are included for this person as they were censored for time to delivery.*P-value from Log-rank tests, profile likelihood confidence intervals reported for 95% CI of HR.

P-value for non-inferiority hypothesis based on Cox proportional hazards model (H_0: HR $\leq$ 0.74 vs. H_A: HR > .74), p-value < .05 provides evidence to reject inferiority and conclude BM is non-inferior to VM.

Table 3: Multiple Cox proportional hazards regression model for time to delivery (oxytocin included as baseline covariate).

(N = 300, 242 vaginal deliveries, Model AIC = 2190.2).

Covariate	Estimate	SE	P Value	HR [95% CI]†	P Value$_{non\text{-}inferiority}$
Dose route (BM vs. VM)	-0.530	0.137	0.0001	**0.59 [0.45, 0.77]**	0.952
Site (Eskenazi vs. Methodist)	0.605	0.149	<0.0001	1.83 [1.37, 2.46]	
Maternal age (y)	0.0003	0.012	0.982	1.00 [0.98, 1.02]	
BMI (kg/m2) ‡	-0.010	0.010	0.294	0.99 [0.97, 1.01]	
Nulliparous (no)	1.17	0.171	<0.0001	3.04 [2.19, 4.26]	
Bishop score	0.158	0.038	<0.0001	1.17 [1.09, 1.26]	
Epidural (no vs. yes)	0.622	0.168	0.0002	1.86 [1.33, 2.57]	
Need for oxytocin (no vs. yes)	1.324	0.154	< 0.0001	3.76 [2.77, 5.08]	

†Profile likelihood confidence intervals.

‡ One person missing BMI, imputed with mean of cohort.

Note: HRs <1.00 should be interpreted as that group needing more time to delivery.

Table S1: Adverse events for women in the IMPROVE study

Adverse Event	*VM group (n= 152)*	*BM group (n= 148)*	*P Value‡*
Maternal adverse events:			
Any maternal adverse event	34 (22.4)	32 (21.6)	0.876
Allergic reaction to misoprostol	0	1 (0.7)	
Tachysystole requiring therapeutic intervention	22 (14.5)	18 (12.2)	
Cesarean for distress	5 (3.3)	14 (9.5)	
Other	9 (5.9)	3 (2.0)	
Fetal adverse events:			
Any fetal adverse event	50 (32.9)	51 (34.5)	0.774
APGAR score at 5 minutes <7	12 (7.9)	8 (5.4)	
Cord gas pH <7.00	2 (1.3)	3 (2.0)	
Unexpected admission to NICU*	20 (13.2)	21 (14.2)	
Other	26 (17.1)	29 (19.6)	
Maternal Serious adverse events:			
Any serious adverse event	9 (5.9)	11 (7.4)	0.461
Uterine rupture	0	0	
Maternal death	0	0	
Persistent or significant disability/incapacity	0	0	
Inpatient or post-partum hospitalization**	8 (5.3)	11 (7.4)	
Other life threatening event	1 (0.7)	0	

All data are presented as no. (%)

‡ P-Values obtained from Chi-square test. * Unexpected admission to NICU for condition identified after administration of first dose of study drug. ** Inpatient readmission postpartum or prolongation of existing hospitalization

Table S2: Multiple Cox proportional hazards regression model for time to delivery (Oxytocin included as time-varying covariate, 0 before receipt, 1 at time of receipt).

(N = 300, 242 vaginal deliveries, Model AIC = 2244.1).

	Estimate	SE	P value	HR [95% CI]†	P value$_{non\text{-}inferiority}$
Dose route (buccal vs. vaginal)	-0.568	0.137	<0.0001	**0.57 [0.43, 0.74]**	0.975
Site (Eskenazi vs. Methodist)	0.347	0.147	0.018	1.41 [1.37, 2.46]	
Maternal age (y)	-0.0002	0.012	0.988	1.00 [0.98, 1.02]	
BMI (kg/m2) ‡	-0.019	0.010	0.055	0.98 [0.96, 1.00]	
Nulliparous (no)	1.113	0.169	<0.0001	3.04 [2.19, 4.26]	
Bishop score	0.146	0.040	0.0002	1.16 [1.07, 1.25]	
Epidural (no vs. yes)	0.619	0.169	0.0002	1.86 [1.32, 2.56]	
1st dose of oxytocin received (yes vs. no)	0.521	0.156	0.0008	1.68 [1.24, 2.29]	

†Profile likelihood confidence intervals.

‡ One person missing BMI, imputed with mean of cohort.

P-value for non-inferiority hypothesis based on Cox proportional hazards model (H_0: HR $\leq$ 0.74 vs. H_A: HR > .74), p-value < .05 provides evidence to reject inferiority and conclude BM is non-inferior to VM.

Table S3: Time to delivery (hours) by Parity

	Nulliparous Women (N = 124)		
	VM group	BM group	
	n = 59, 18 censored	n = 65, 24 censored	P Value†
Time to delivery (hours)–			
Median [95% CI]	33.4 [27.5, 37.7]	32.7 [28.0, 39.7]	0.912
	Multiparous Women (N = 176)		
	VM group	BM group	
	n = 93, 6 censored	n = 83, 10 censored	P Value†
Time to delivery (hours)–			
Median [95% CI]	16.7 [15.0, 18.2]	23.4 [20.3, 28.2]	<.0001

†Estimates obtained from Kaplan-Meier method and results of Log-rank test.

Table S4: Multiple Cox proportional hazards regression models for time to delivery fit separately by Parity

Nulliparous (YES) (N = 124 women, 82 vaginal deliveries)	Estimate	SE	P Value	HR [95% CI]†
Dose route (BM vs. VM)	0.116	0.230	0.613	**1.12 [0.72, 1.77]**
Site (Eskenazi vs. Methodist)	0.316	0.259	0.223	1.37 [0.83, 2.31]
Maternal age (y)	0.023	0.023	0.305	1.02 [0.98, 1.07]
BMI (kg/m2) ‡	-0.018	0.018	0.309	0.98 [0.95, 1.02]
Bishop score	0.210	0.073	0.004	1.23 [1.07, 1.42]
Epidural (no vs. yes)	0.878	0.427	0.040	2.41 [0.98, 5.32]
Need for oxytocin (no vs. yes)	1.224	0.295	< 0.0001	3.40 [1.87, 5.98]
Nulliparous (NO) (N = 176 women, 160 vaginal deliveries)	Estimate	SE	P Value	HR [95% CI]†
Dose route (BM vs. VM)	-0.815	0.174	<0.0001	**0.44 [0.31, 0.62]**
Site (Eskenazi vs. Methodist)	0.747	0.187	<0.0001	2.11 [1.46, 3.05]
Maternal age (y)	-0.01	0.015	0.508	0.99 [0.96, 1.02]
BMI (kg/m2) ‡	-0.012	0.012	0.322	0.99 [0.97, 1.01]
Bishop score	0.148	0.050	0.003	1.16 [1.05, 1.28]
Epidural (no vs. yes)	0.603	0.188	0.001	1.83 [1.25, 2.62]
Need for oxytocin (no vs. yes)	1.323	0.188	< 0.0001	3.75 [2.59, 5.42]

†Profile likelihood confidence intervals.

‡ One person missing BMI, imputed with mean of cohort.

Table S5: Post-Delivery Satisfaction Questionnaire

Participant Questionnaire		**Route of Misoprostol**		
1. How did you feel about your experience with your induction of labor?	Overall (n = 300)	VM (n = 149)	BM (n = 141)	P value†
It was a great experience	156 (52.0)	79 (53.0)	77 (54.6)	0.259
It was a terrible experience	23 (7.7)	15 (10.1)	8 (5.7)	
It was neither great nor terrible	98 (32.7)	51 (34.2)	47 (33.3)	
I'm not sure	13 (4.3)	4 (2.7)	9 (6.4)	
Missing	10 (3.3)	-	-	
2. How painful did you feel that your induction was?		(n = 148)	(n = 142)	
It was less painful than I expected	89 (29.7)	46 (31.1)	43 (30.3)	0.410
It was more painful than I expected	78 (26.0)	35 (23.7)	43 (30.3)	
It was about what I expected	123 (41.0)	67 (45.3)	56 (39.4)	
Missing	10 (3.3)	-	-	
3. Which way of receiving the medication was more comfortable?		(n = 146)	(n = 138)	
Getting the tablet in my vagina	39 (13.0)	26 (17.8)	13 (9.4)	0.122
Getting the tablet in my cheek	116 (38.7)	57 (39.0)	59 (42.8)	
They both were the same	129 (43.0)	63 (43.2)	66 (47.8)	
Missing	16 (5.3)	-	-	
4. Which method of getting the medication did you like better?		(n = 146)	(n = 139)	
Getting the tablet in my vagina	74 (24.7)	37 (25.3)	37 (26.6)	0.202
Getting the tablet in my cheek	115 (38.3)	53 (36.3)	62 (44.6)	
No preference	96 (32.0)	56 (38.4)	40 (28.8)	
Missing	15 (5.0)	-	-	

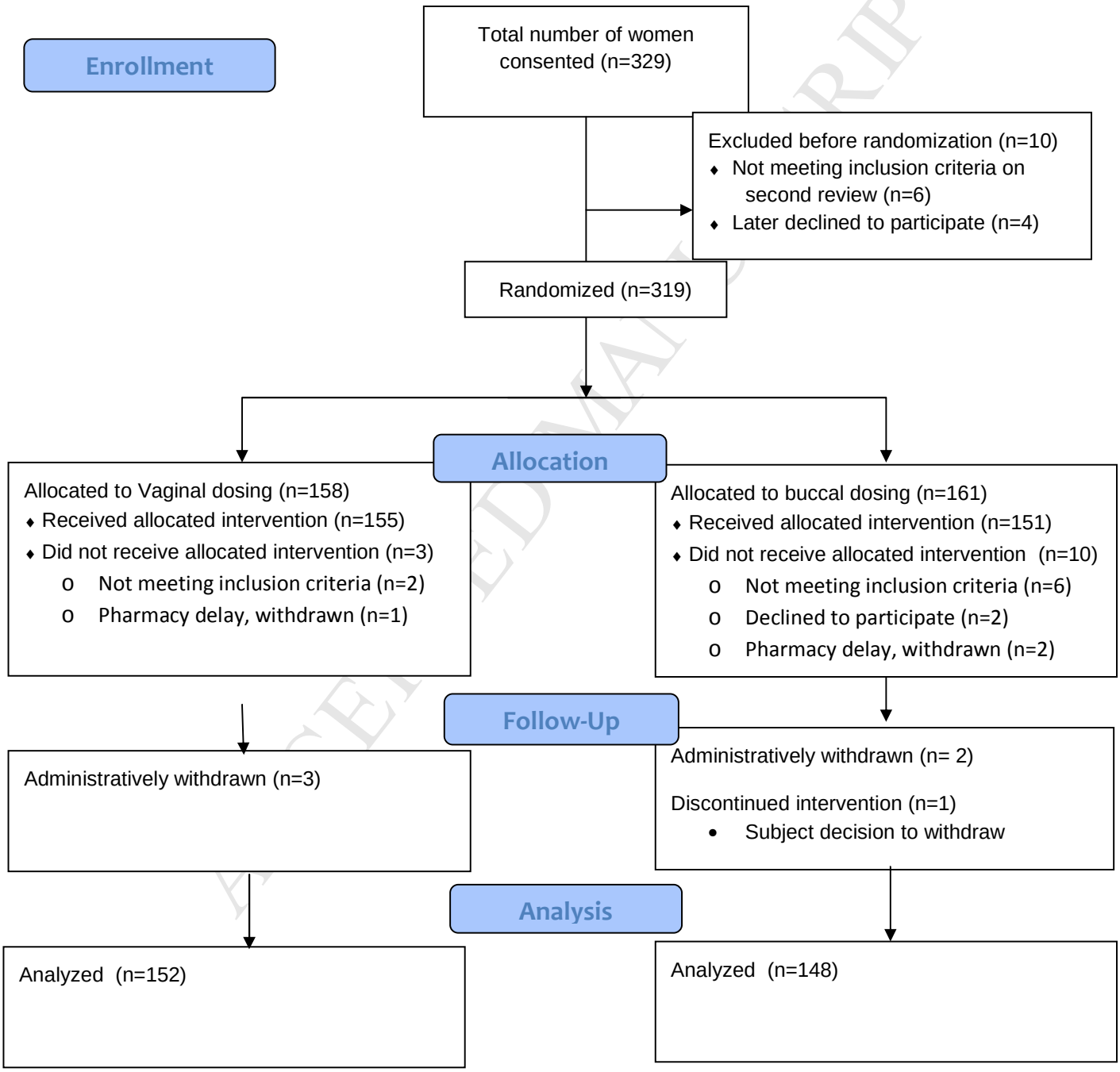
5. If you were to have an induction of labor in the future, which one would you prefer?		(n = 145)	(n = 139)	
I would rather have the medication in my vagina	94 (31.3)	56 (38.6)	38 (27.3)	0.096
I would rather have the medication in my cheek	125 (41.7)	56 (38.6)	69 (49.6)	
I'm not sure	65 (21.7)	33 (22.8)	32 (23.0)	
Missing	16 (5.3)	-	-	

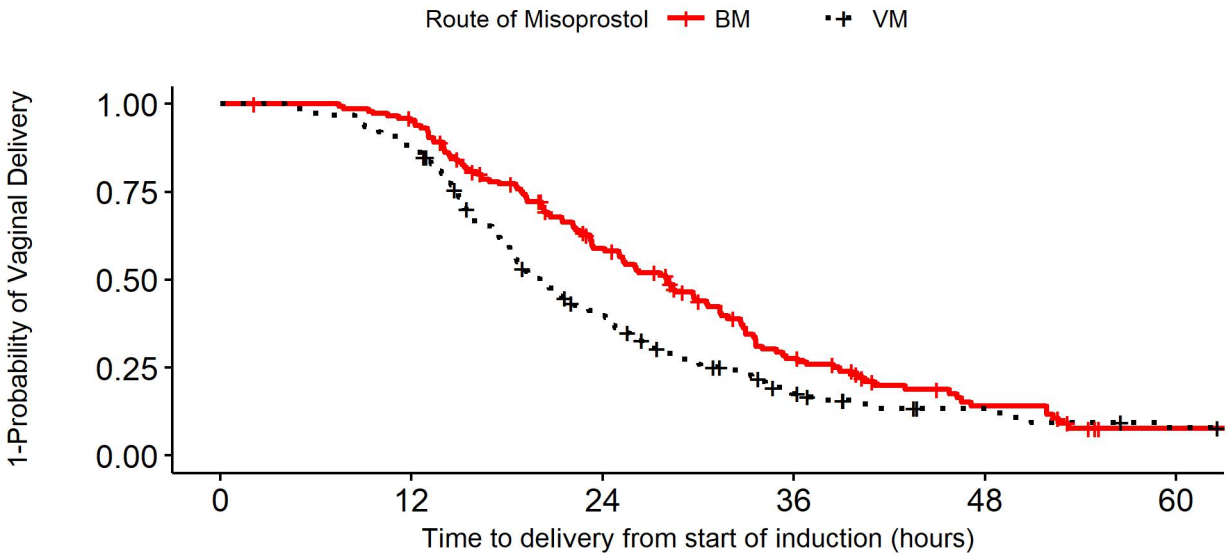
All data are presented as no. (%)

†Chi-square test.

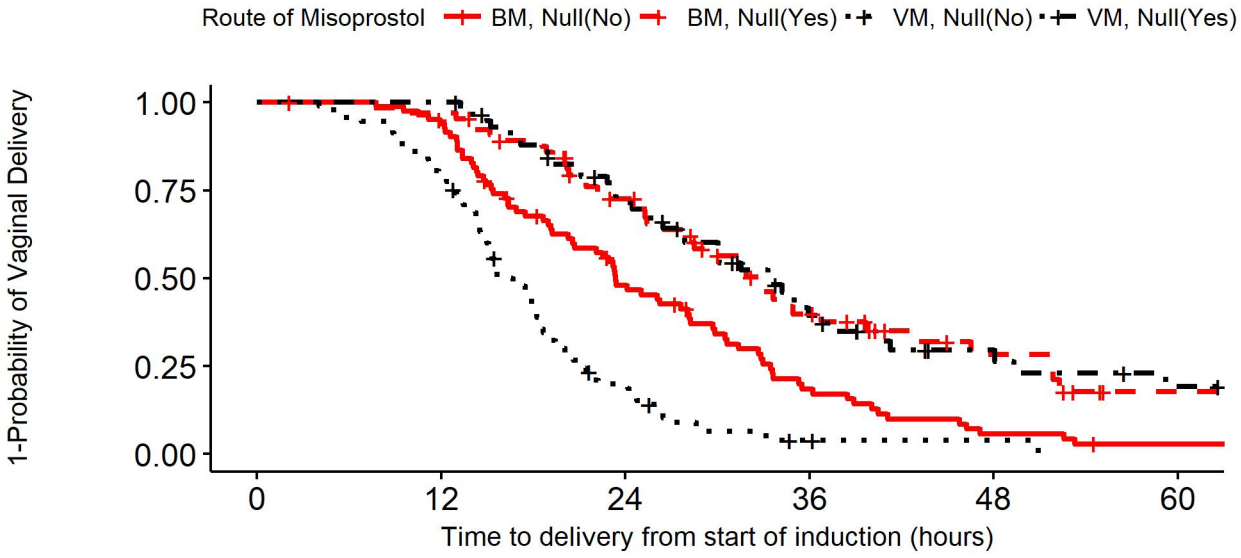
CONSORT
TRANSPARENT REPORTING of TRIALS

Figure 1: IMPROVE Trial CONSORT Flow Diagram





BM	148	139	78	32	12	2
VM	152	132	56	20	10	5



BM, Null(No)	83	76	36	13	4	1
BM, Null(Yes)	65	63	42	19	8	1
VM, Null(No)	93	73	17	2	1	0
VM, Null(Yes)	59	59	39	18	9	5

Supplementary Appendix Material

Full IMPROVE Study Methods Details

Participants

Women who presented to one of the two labor and delivery units for delivery who required cervical ripening were eligible for the trial. If the provider was considering using misoprostol for cervical ripening, the women who met inclusion/exclusion criteria were approached by study personnel. Women had to be undergoing either a medically indicated induction of labor at a gestational age beyond 37 $^{0/7}$ weeks OR an elective induction of labor after 39 completed weeks, be at least 14 years-old, with a singleton pregnancy in the cephalic presentation confirmed by either physical examination or ultrasound. Women had to have a modified Bishop score ≤ 6 (commonly used as a cutoff for the need for cervical ripening). Women were excluded if they had a known prior uterine scar, untreated cervical infection, known major fetal congenital anomaly, or evidence of fetal compromise (Category 2 or 3 fetal tracing) before the start of the induction. Women were also excluded if they had a known allergy to misoprostol, had a planned cesarean delivery, had undergone a prior induction or cervical ripening measures during the current pregnancy, or had any other contraindication to labor induction or misoprostol therapy.

All women underwent the informed consent process in English or Spanish (utilizing either a bilingual research team member or a hospital provided interpreter) and provided written informed consent prior to study procedures.

Study drugs and preparation

Misoprostol tablets (25 and 50 microgram doses) were obtained from the manufacturer (Novel Laboratories, Somerset, NJ). Identical placebo tablets were obtained from University of Iowa Pharmaceuticals. Prepared placebo tablets were tested for stability, dissolving characteristics, and other characteristics to match the misoprostol tablets as closely as possible. Details on the placebo preparation and testing are available upon request.

The tablets were prepared for distribution by the Investigational Pharmacies of the 2 hospitals in the same way. For women who would be randomized to the “vaginal misoprostol” group, the appropriate

dose of misoprostol was placed in a foil packet labeled with the study ID number, dosing time, and "Vaginal". An identical placebo pill was prepared in a foil packet labelled in the same way but with the words "Buccal" on the label. Similarly, for women randomized to the "buccal misoprostol" group, the appropriate dose of misoprostol was placed in a foil packet labelled with the study ID number, dosing time, and "Buccal". An identical placebo pill was prepared in a foil packet labelled in the same way but with the words "Vaginal" on the label. Thus, at each study drug dosing time, the participant had one packet with a tablet for placement in the vagina and one for placement in the buccal mucosa.

Randomization and allocation concealment

Stratified randomization with blocks of size 10 was used to create a separate randomization list for each hospital with 1:1 assignment to treatment group by the study statistician. The computer-generated randomization list was then provided to the Investigational Pharmacy at both hospitals. The Investigational Pharmacy at each hospital prepared packages as described which were to be sent to the labor and delivery unit for use. After informed consent was obtained by the study team, the appropriate Investigational Pharmacy was notified. The pharmacist on duty obtained the next sequentially numbered study drug packet and sent it to labor and delivery.

Blinding

This was a triple-blind study. Other than the investigational pharmacists, who did not have direct participant interaction, all study investigators and clinical care providers were blinded to the allocation of the participants. All clinical care was thus per standard care protocols for all participants. As the participant received a tablet placed in the vagina and an identical tablet in the buccal mucosa at the same time, participants were unaware of their assignment. The data collectors/outcomes assessors similarly collected all data and outcomes unaware of the assignment. All interim safety analyses and reports to the Data Safety Monitoring Board were blinded with the groups reported only as "A" and "B".

Study procedures

On presentation for labor induction, clinical evaluation and decision to use misoprostol, the study team confirmed that the woman met inclusion/exclusion criteria, obtained informed consent, and recorded

baseline data and participant characteristics. The pharmacy was contacted and notified the woman was enrolled in the IMPROVE trial. The pharmacy then sent the "Vaginal" and "Buccal" study drugs to labor and delivery for use by the participant. The pill marked "Buccal" was placed between the teeth and mucous membrane of the cheek. A visual aid was used to show the woman the proper placement. They were instructed not to disturb the tablet as it dissolves. A small snack with liquid was allowed before each buccal dose if the woman desired. If tablet remained undissolved after 30 minutes, the woman was instructed to swallow the remainder of the tablet. The tablet marked "Vaginal" was placed by the clinical care provider (physician or midwife) high into the posterior vaginal fornix. The provider placing the drug was able to use water-based lubricating jelly to facilitate the examination and decrease participant discomfort according to standard local practice. The initial dose of misoprostol used in this protocol was 25 mcg. Subsequent doses, if utilized, were 50 mcg. This is an accordance with the ACOG Practice Bulletin on misoprostol for labor induction.[2]

Throughout the cervical ripening and induction process, continuous external electronic fetal monitoring was utilized as per standard hospital obstetric practice. Other forms of monitoring were permitted including intrauterine pressure catheters if deemed clinically necessary.

Subsequent to the initial cervical examination, follow up cervical examinations were performed approximately every four hours, prior to buccal and vaginal administration of the next dose. An additional dose of study drug was given if sufficient cervical ripening had not been achieved (Bishop Score $\leq$6), the fetal tracing was not currently category 2 or 3, there was no evidence of tachysystole, and there had been no adverse reactions to the study drug. These continuation criteria were designed to mimic clinical scenarios where additional doses of misoprostol are used. The next dose of study drugs was thus administered only if there is not an adequate response (not contracting adequately to achieve active labor) to the prior dose per the provider and there was no evidence of fetal nonreassurance. After the initial dose of 25mcg, the second and any subsequent doses were 50mcg. Doses above 50mcg were not used for this study. Any cervical examinations performed for clinical indications and examinations after discontinuation of the drug until the time of delivery were also recorded.

If, after at least 4 hours another dose of study drug was deemed to be indicated by the care provider, the pharmacy was contacted and the next dose of that participant's study drugs was sent to labor and delivery for use. Study participation and drug placement continued until: 1) there was adequate response and cervical ripening was no longer needed, 2) there were signs of tachysystole, non-reassuring fetal heart tracing, or other adverse event that would make the provider stop the misoprostol, or 3) 24 hours of study drug had been given (maximum of 7 doses). At that time, the reason for stopping the study (or completion of study procedures) was noted and the clinical provider proceeded with the labor induction or augmentation as clinically warranted. After cervical ripening was complete or the participant was taken off of the study, there were no limitations placed on the clinical care of the participant and they were managed in the usual fashion, allowing augmentation and other procedures deemed needed to accomplish delivery. Any interventions subsequent to placement of the first dose of study drug were recorded for later analysis.

Outcomes assessment

The primary outcomes for the IMPROVE trial involve both efficacy and safety. The primary efficacy outcome was the time to delivery, defined as the time from placement of the first dose of study drug to the time of delivery. This study was planned to determine if BM could be considered non-inferior to VM in time to delivery. The primary safety outcome was the rate of cesarean delivery performed urgently for fetal non-reassurance as the primary indication. Secondary efficacy outcomes included: rate of vaginal delivery within 24 hours of the induction beginning, number of doses needed of misoprostol for the induction, maximum/total dose of oxytocin utilized for uterine stimulation, and other drugs used for cervical ripening or induction of labor after beginning the study drug. The secondary safety outcomes assessed were: uterine tachysystole requiring therapeutic intervention, uterine rupture, maternal or fetal death, prolonged inpatient hospitalization or new postpartum hospitalization, unexpected NICU admission, neonatal cord blood gases (if obtained), Apgar score, birth weight, and rate of chorioamnionitis.

In an effort to obtain data on women's preferences for route of receiving misoprostol, the IMPROVE trial assessed participant satisfaction with a patient satisfaction tool obtained from the Nassar study[9] with some customization based on local practices. In short, the women were typically asked to complete the survey on the postpartum ward the first or second day after the baby was born. This was available in both English and Spanish. They were asked to rate the discomfort they experienced with the vaginal and buccal routes and which route they would prefer if both routes were equal in efficacy and safety and they needed to be induced again.

At least 30 days after delivery, the medical records of the participant and the newborn were reviewed and data abstracted from the medical record to capture all relevant maternal and newborn outcomes and complications.

Statistical analysis and sample size calculations

A sample size of 300 women with 260 expected vaginal deliveries (87%, based on prior induction data in our hospital) was estimated to have 80% power to test for non-inferiority of time to delivery of buccal misoprostol (BM) with a null hypothesis that the hazard ratio of BM relative to VM (HR) ≤ 0.74 vs alternative hypothesis that the HR > 0.74 with type I error set at 0.05. This non-inferiority margin was derived from retrospective data on time to delivery by both routes, which equated to approximately a 4.5 hour difference in median time to delivery. For all other outcomes, the two-sided superiority p-values are provided.

All analyses were performed according to the intention-to-treat principle. Participant and delivery characteristics were compared between treatment groups using appropriate tests (T-test, Wilcoxon rank sum test, Chi-square test, or Fisher's exact test). Chi-square tests were performed to compare participant satisfaction survey questions between treatment groups. For the primary outcome of time to delivery, median time to delivery and associated 95% confidence intervals (CI) were estimated by Kaplan-Meier method for the overall cohort and by route of delivery (buccal [BM] or vaginal [VM]). Women who required cesarean were censored at the time of cesarean and those that did not deliver vaginally during the hospital admission were censored at the time of discharge. Cox proportional hazards

regression was used to estimate the HR for BM relative to VM for delivering vaginally and associated 95% CI. The test of non-inferiority which is testing the hypothesis H_0: HR ≤ 0.74 vs. H_A: HR > .74 was obtained from this model. A p-value < .05 provides evidence to reject inferiority and conclude the buccal route of dosing is non-inferior to the vaginal route.

In secondary analyses, the HR and associated 95% CI for route of misoprostol was also estimated from the Cox proportional hazards regression, adjusting for covariates known to be associated with time to delivery. Additional analysis included checking the proportional hazards assumption by including two-way interactions between each covariate and the log of time to delivery, checking for heterogeneity in treatment effect by examining two-way interactions between treatment effect and each covariate and including receipt of oxytocin as a time-varying coefficient in the full proportional hazards model. These results led to a subgroup analysis which was completed for the primary outcome to examine the treatment effect by parity (nulliparous vs. multiparous). Outcomes were evaluated at a 0.05 level of significance. All analyses were completed with SAS software version 9.4 (SAS Institute, Inc. Cary, NC)

Results- Full reporting of Cox proportional hazard and adjusted models

Covariates known to be associated with time to delivery were included in a full Cox proportional hazards model to estimate the adjusted HR for BM vs. VM for time to delivery (Table 3). Covariates included are study hospital site, maternal age, BMI at time of admission, parity, Bishop Score at entry, use of epidural, and need for oxytocin. Based on this model, women more likely to delivery vaginally were from the Eskenazi study site, were multiparous, had a higher baseline Bishop score, did not receive an epidural, and did not require oxytocin. In the adjusted full model, the BM vs. VM adjusted HR is 0.59, 95% CI, 0.45 to 0.77, p<0.0001; Table 3). Thus, VM was still found to be superior even with adjustment for covariates. Thus we still cannot conclude that BM is non-inferior to VM for time to delivery ($P_{non\text{-}inferiority}$ = 0.952). Although the assumption of proportional hazards was not rejected for this full model (P=0.062), the two-way interaction between parity and log of time to delivery and oxytocin and log of

time delivery were both significant at the .05 level. Thus we ran additional models to examine these important covariates.

For oxytocin, rather than include an indicator of whether women required oxytocin at any time during delivery in the model, we included oxytocin as a time-varying indicator with 0 prior to the first dose of oxytocin, and 1 following receipt of the first dose. Based on this model, the BM vs. VM adjusted HR is 0.57, 95% CI, 0.43 to 0.74, which is similar to the primary model with oxytocin as a baseline covariate (Supplementary Table S2). Also, covariate results were similar to the primary model except BMI, which trended towards significance (P=0.055). Based on the Akiake information criterion (AIC), with lower values indicating better fit, the first model with oxytocin as a baseline covariate is a better model (2190.2 vs. 2244.1, respectively) thus model results with oxytocin as time-varying are included in Supplementary Table S2.

We ran the full model and checked the two-way interaction between each covariate and treatment separately. The only two-way interaction found to be statistically significant was between treatment and indicator for nulliparous women (P =0.0007), indicating that the treatment effect for time to delivery varies by parity. Thus a subgroup analysis was conducted for time to delivery by whether or not women were nulliparous (Supplementary Table S3, Figure 2 – Bottom Panel). Among nulliparous women, there was not a significant difference in median time to delivery between treatment groups (VM median 33.4 hours, 95% CI, 27.5 to 37.7 hours vs BM median 32.7 hours, 95% CI, 28.0 to 39.7 hours, P=0.912). However, there was a large difference between treatment groups in median time to delivery for multiparous women (VM median 16.7 hours, 95% CI, 15.0 to 18.2 hours vs. BM median 23.4 hours, 95% CI, 20.3 to 28.2 hours, P<0.0001). Additionally we ran the full model adjusting for covariates separately for nulliparous and multiparous women (Supplementary Table S4). For nulliparous women, even after adjusting for covariates there was not a significant difference in time to delivery between treatment groups (BM vs. VM adjusted HR is 1.12, 95% CI, 0.72 to 1.77, P=0.613). For multiparous women, BM vs. VM adjusted HR is 0.44, 95% CI, 0.31 to 0.62, P<0.0001; thus for multiparous women, the vaginal route of delivery of misoprostol was clearly superior to the buccal route of delivery.